REMARKS

1. Status of the Claims

Claim 2 is amended to change the transitional claim phrase from "consisting essentially of" to "consisting of". Support for this modification is found e.g. on page 5, lines 29-31 of the application as filed.

Claims 2 and 7-11 are amended such as to replace the expression "immunoglobulins G composition" by the expression "immunoglobulin G composition".

Claim 11 is amended such that the term 'dimmers" is replaced by the term "dimers".

2. Claim Rejection under 35 U.S.C. § 102(b)

Claims 2, 3, 5, 7, 9 and 11 are rejected by the Examiner under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,945,098. The Examiner in particular considers that the expression "consisting essentially of" includes other components in addition to the recited sugar alcohol, glycine and non-ionic detergent. Applicant respectfully disagrees for the following reasons.

Applicant submits that claim 2 as amended now recites a stabilizing composition consisting of a sugar alcohol, glycine and a non-ionic detergent. According to amended claim 2, compounds such as PEG or sugars other than sugar alcohols (e.g. maltose or sucrose) are excluded from the scope of the composition defined by the claims.

US 5,945,098 discloses compositions for stabilizing immunoglobulins under liquid form (see column 3, lines 62-63), and comprising at least a non-ionic detergent (see column 4, lines 44-46), and one or more amino acids, preferably selected among glycine, lysine, arginine and phenylalanine (see column 5, lines 12-17). The disclosed stabilizing composition might further comprise additives used to adjust the isotonicity, such as further amino acids, carbohydrates and/or physiologically acceptable salts (see column 5, lines 32-37), and polyvinylpyrrolidone (PVP) (see column 5, lines 19-23). Finally, US 5,945,098 discloses that polyethylene glycol

The examples of US 5,945,098 are more specifically drawn to compositions comprising glycine, PEG and polysorbate 80 (see example I); glycine and polysorbate 80 (see example II); glycine, PEG, polysorbate 80 and citrate or phosphate buffer (see example III); glycine, PVP, PEG and polysorbate 80 (see example IV); and glycine, carbohydrates, PEG and polysorbate 80 (see example V).

US 5,945,098 nevertheless fails to explicitly disclose any stabilizing composition consisting of the specific combination of a sugar alcohol, a non-ionic detergent and glycine, as claimed in the present invention. Applicant submits in particular that the '098 patent teaches that all carbohydrates are regarded as equivalent additives for stabilizing immunoglobulin compositions in (see in particular column 5, lines 37-40 and column 7, example V, lines 9-12); whereas the present inventors have surprisingly discovered that only sugar alcohols, and preferably mannitol, are suitable for use in the stabilizing composition of the invention. Further, it clearly appears in the present application clearly teaches that stabilisers such as PEG are to be avoided, since they are known to behave as a precipitating agent upon lyophilization.

The subject matter of claim 2, and thus of claims 3-5 and 7-11 is thus novel with respect to the disclosure of US 5,945,098.

3. Claim Rejection under 35 U.S.C. § 103 (a)

Claims 2-5 and 7-11 are rejected by the Examiner under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 4,597,966, in view of EP 0 392 717 and US Patent Application No. 2006/0246060. This rejection is respectfully traversed.

The Examiner considers in particular that US 4,597,966 teaches a stabilizing IgG formulation comprising IgG, histidine, and glycine at a concentration of about 0.1M, and that it would have been obvious for the skilled person in the art to add mannitol at the concentration as taught by EP 0 392 717, and a non-ionic detergent as taught in US 2006/0246060 to the disclosed formulation for obtaining the composition of the present invention.

Applicant respectfully disagrees for the following reasons.

US 4,597,966 teaches a stabilizing formulation comprising IgG, histidine and glycine at a concentration of about 0.1M. This patent nevertheless fails to disclose or even suggest any formulation further comprising a sugar alcohol and a non-ionic detergent. Applicant in particular submits that the stabilizing properties of the formulation disclosed in US 4,597,966 are clearly disclosed as arising primarily from the presence of histidine, since this amino acid is considered to be the only one suitable for adequately buffering an aqueous solution against undesirable changes in hydrogen ion concentration (pH). See in particular in column 5, lines 31-34, and lines 39-42:

> *"The buffering capacity in the present preparations is believed to be provided for the most part by histidine, the only amino acid with significant buffering capacity in the desired range". (emphasize added)*

Therefore, whereas US 4,597,966 actually discloses that the combination of histidine with glycine might result in further enhanced stabilizing properties of the formulation (see column 4, lines 62-64, column 8, lines 29-31), it nevertheless unambiguously appears that the use of glycine alone as a stabilizer is heavily criticized, if not strongly unrecommended. See in particular in column 10, lines 54-57:

> *"Table demonstrate that a glycine-saline buffer is not adequate for the stabilization of purified liquid gamma globulin products were the protein concentration is relatively low",*

in column 11, lines 32-34:

> *"The data in Table IV demonstrate that the buffering capacity of the standard glycine-saline buffer is inadequate for the tested protein concentrations.",* and

in column 11, lines 58-61:

> *"The data in Table V shows that within the range of glycine concentrations of about 0.01M to about 0.5M the stabilizing effect of the present solutions is not dependent upon glycine concentration."*

As a result one skilled in the art, in view of the teachings of US 4,597,966, would not have been motivated to prepare the composition claimed in the present application, and also would not have been motivated to use glycine without histidine for stabilizing immunglobulins formulations.

Applicant further submits that EP 0 392 717 fails to cure the deficiencies of US 4,597,966.

EP 0 392 717 indeed teaches pharmaceutical formulations for stabilizing immunoglobulin conjugates, which contain mannitol and glycine. This document demonstrates in particular that a formulation containing an immunoglobulin conjugate, glycine and mannitol in a 1:1:1 weight ratio reduces the aggregation of said conjugates upon liquid storage or lyophilization. EP 0 392 717 nevertheless fails to disclose any formulation containing a non-ionic detergent. In view of the combined teachings of US 4,597,966 and EP 0 392 717, and considering the fact that none of these documents actually teach or even suggest the use of a non-ionic detergent, Applicant thus submits that a person skilled in the art would never have been motivated to prepare the stabilizing formulation claimed in the present invention. Further, the Examiner will note that, as discussed above, US 4,597,966 unambiguously teaches that the combination of histidine with glycine provides enhanced stabilizing properties and that histidine remains indispensable as a stabilizer, in particular for low concentrations of immunoglobulins. It therefore results that in view of US 4,597,966 and EP 0 392 717, the person skilled in the art would never have been motivated to prepare a stabilizing formulation which does not comprise histidine, since this would have resulted in significantly less effective stabilizing properties.

Finally, Applicant submits that US 2006/0246060 fails to cure the deficiencies of US 4,597,966 in view of EP 0 392 717.

US 2006/0246060 teaches formulations for stabilizing an immunoconjugate and an antibody, comprising a buffer, a polyol (preferably sucrose or trehalose) and optionally a non-ionic surfactant such as polysorbate. As disclosed explicitly in this document, in particular at page 1, left column, [0004] and [0005], the polyol, and preferably sucrose, is systematically incorporated in the formulation, should the later be under an aqueous form or a lyophilized form, since the tonicifying action of polyols is requested for stabilizing said formulations (see in particular page 2, right column, [0020]). On the contrary, the non-ionic surfactant is regarded as an optional

compound providing additional stability to the solutions under their aqueous form (see in particular at page 1, [0006] and page 3, right column, lines 5-8). As a result, the person skilled in the art, in view of the teachings of US 2006/0246060 would unambiguously have considered that polyols (and more specifically sucrose) are indispensable for stabilizing immunoglobulin solutions both under liquid and lyophilised forms, and would never have reasonably considered using the non-ionic surfactant alone within the stabilizing formulations disclosed in US 4,597,966, even in view of EP 0 392 717.

Applicant therefore submits that the Examiner is wrong in supposing that, in view of the cited documents US 4,597,966, EP 0 392 717 and US 2006/0246060, the person skilled in the art wanting to prepare a more efficient stabilizing composition would have intentionally decided to prepare a composition consisting only of a sugar alcohol, glycine and a non-ionic surfactant, thereby deliberately avoiding to use histidine and sucrose, which are referred to as indispensable stabilizing compounds. In preparing a stabilizing composition composed only of stabilizing compounds which are disclosed as "additional" in the cited prior art, the person skilled in the art would never have been motivated with any reasonable expectation of success to prepare a composition enabling the efficient stabilization of immunoglobulins both under liquid and lyophilized forms.

The subject matter of claim 2, as well as of claims 3-5 and 7-11 is thus inventive and not obvious over the teachings of US 4,597,966, in view of EP 0 392 717 and further in view of US 2006/0246060.

Withdrawal of the corresponding rejection is thus respectfully requested.

In view of the above amendment, applicant believes the pending application is in condition for allowance.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Leonard R. Svensson Reg. No. 30,330 at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

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Respectfully submitted,

By: _____

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